



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No. : 09/806,368
Applicant : Mieko KATSUURA et al
Filed : September 20, 2001
TC/A.U. : 1647
Examiner : Rachel B. Kapust

Docket No. : 2923-0581

Customer No. : 6449

Confirmation No. : 8538

Title : BONE MORPHOGENETIC PROTEIN ANTAGONIST BASED ON THE MATURE PROTEIN

RESPONSE TO RESTRICTION REQUIREMENT

Director of the United States Patent
and Trademark Office
P.O. Box 1450
Alexandria, Virginia 22313-1450

December 2, 2003

Sir:

In response to the Restriction Requirement of October 2, 2003, applicants hereby elect group I, claims 1, 2, 4, 6, 8, 12 and 13 with traverse on the grounds that the proteins are structurally related and have a common antagonistic mechanism which is different from the prior art mechanism described in Hirsinger et al.

Applicants respectfully point out that no unity of invention objections were raised during the international phase of the present PCT application because all of the claims are linked by a common inventive feature. The claimed proteins all show particular modifications in the amino acid sequence compared to the major human proteins from which they were derived. In the claimed proteins, tryptophane or methionine residues are replaced or modified as compared with

the naturally occurring proteins. This modification results in an antagonistic activity against morphogenic bone proteins. Though the mature human proteins from which the claimed proteins are derived differ in amino acid sequence, they are structurally very similar to each other due to 7 cysteine residues in comparable positions.

Members of the TFG- β -superfamily to which all 4 proteins (MP52, BMP-2, BMP-4 and BMP-7) belong (cf. page 1 bottom of the description) form a very similar 3D-structure due to their 7 cysteines with 3 intra-and one intermolecular disulfide bridge. The high homology on the amino acid level, a similar structure and the overlapping use of receptors makes clear why the specific modifications of only methionines or tryptophanes can result in an antagonistic effect with all 4 proteins and why the modified MP52 has an antagonistic effect for MP52 and for BMP-2 (cf. Figure 2). The high homology is also clear from the fact that all 4 proteins contain tryptophanes at the corresponding positions as shown in an alignment of the sequences (cf. page 9, line 8 of the description).

The Office Action, cites Hirsinger et al. for the contention that having an antagonistic activity against bone morphogenetic proteins is not an inventive concept. While it is known that there are naturally occurring proteins which have an antagonist effect on BMPs by binding to BMP, for example, the present application is based on a different antagonistic principle. The proteins Noggin, Chordin and Follistatin, which are disclosed in Hirsinger et al., are naturally occurring proteins (not BMPs) having the functional feature of binding BMP (specifically extracellularly) and thus avoiding interactions with BMP-receptors

(cf. Hirsinger et al., page 4605-4606, which states "*These molecules [Noggin, Chordin or Follistatin] have been shown to directly antagonize BMP-4 by binding to this protein and preventing an interaction with its receptor*"). However, in the present application, the BMP protein itself in a slightly modified form is the antagonist instead of a different protein which binds BMPs. The modified, inactive BMP of the present invention directly binds to BMP receptors (cf. page 6, lines 18-19, and page 7, lines 1-4), instead of the receptors binding to the natural BMP and thus there is basically no signal transduction. This antagonistic mechanism is clearly different from the mechanism shown in Hirsinger et al. where the molecules bind to the BMP itself thereby preventing interaction with the receptor.

In summary, all of the proteins of the present application are BMP proteins that are modified in a similar manner so that they have the same antagonistic mechanism of action. In view of this, applicants request that the restriction requirement be withdrawn. If the restriction requirement cannot be withdrawn, applicants request that it be modified so that claims 1-8 and 12-13 are examined together. Applicants point out that claims 2-8 show specific examples of the modified human morphogenic protein of claim 1. All of these proteins are derived from MP52 and thus should be examined together.

Applicants note that the restriction requirement does not include claims 14 and 15 which were submitted with the preliminary amendment filed on March 28, 2001. Applicants request clarification as to the status of claims 14 and 15.

In the event this paper is not considered to be timely filed, the Applicants respectfully petition for an appropriate extension of time. Any fee for such an extension together with any additional fees that may be due with respect to this paper, may be charged to Counsel's Deposit Account No. 02-2135.

Respectfully submitted,

By



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